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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/247,054	02/09/99	ANTONIOU M	CACO-0045

HM12/0315

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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	9

DATE MAILED: 03/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/247,054	Antoniou et al.
Examiner	**Group Art Unit**
Anne-Marie Baker, Ph.D.	1632

☒ Responsive to communication(s) filed on *Dec 13, 1999* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-21, 23, and 25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21, 23, and 25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed December 13, 1999 (Paper No. 7) has been entered. Claims 1, 5, 12, 14, 16, and 25 have been amended. Claims 22 and 24 have been cancelled.

Claims 1-21, 23, and 25 are pending in the instant application.

The following rejections are reiterated and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 14, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 14, and 16 are indefinite in their recitation of "wherein the component of an LCR is a component of the β-globin LCR HS3 and HS4" and "wherein the component of an LCR is a component of the β-globin LCR HS3" because it is unclear what component of HS3 or HS4 is being referred to. The claims have been amended to remove the phrase "consisting essentially of" but the claim amendment leaves it unclear what component is specifically referred to in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-14, and 16-21 are rejected under 35 U.S.C. 103(a), for reasons of record advanced on pages 9-11 of the previous Office Action mailed 7/9/99 (Paper No. 5), as being unpatentable over Yates et al. (1985), Sadelain et al. (1995), Greaves et al. (1989), Grosveld et al. (1987), Ustav et al. (1991), and Svensson et al. (1996).

The claims are drawn to a self-replicating episomal DNA expression vector for expressing a gene of interest in a host cell in a tissue-restricted manner wherein the vector comprises a self-replicating origin of replication and a locus control region.

Applicants argue that the Examiner failed to establish the motivation to modify the references to yield Applicants' invention. However, the stated rejection pointed out that LCRs are known in the art and that these genetic regulatory elements have been used in both expression vectors and transgene constructs to provide a tissue-restricted pattern of expression for the operably linked gene. For example, Sadelain et al. (1995) teach a retroviral vector bearing the human β-globin gene and the LCR core sites HS2, HS3, and HS4. The vector confers erythroid-specific expression of the β-globin gene. Furthermore, episomal vectors, such as bovine papillomavirus, are taught in the art as described by Ustav et al. (1991). Thus the genetic elements required to construct the claimed vectors are well-known in the art and only standard molecular biology techniques are required to construct the claimed vectors. The cited references teach that LCR sequences

confer tissue-specific expression in a variety of contexts. Furthermore, Sadelain et al. (1995) specifically point out that "[t]he absence of strictly position-independent expression ... we observe raises the issue of whether the LCR can truly confer position-independent expression when present at one copy per cell ..." One of skill in the art would recognize that episomal vectors could be used to overcome the problems pointed to by Sadelain et al. because episomal vectors are present at more than one copy per cell and do not integrate into the host chromosome, thereby eliminating position effects. Thus, the motivation to combine the cited references is provided by the prior art. Since it would have been desirable to achieve tissue-specific expression using episomal vectors for gene transfer one would have been motivated to incorporate LCR sequences into episomes of various types in order to make gene transfer vectors that replicate independently of the host cell chromosomes and are present at greater than one copy per cell. One would have had a reasonable expectation of success because LCRs have been successfully employed to confer tissue-specific expression of exogenous genes integrated into the host cell chromosome (see e.g. Sadelain et al., p. 6728, column 2, paragraph 2). Furthermore, one would have anticipated a reasonable expectation of success because the function of the genetic elements required to construct the claimed vectors are well-known in the art, as discussed in the previous Office Action (Paper No. 5), and only standard molecular biology techniques are required to construct the claimed vectors. Thus, the motivation to make episomal vectors comprising LCR sequences is provided by the cited art. Applicants have not addressed the stated motivation for using episomal vectors to achieve tissue-specific expression, other than to assert that the cited references do not suggest that it would have been desirable to achieve tissue-specific expression using episomal vectors. However, the cited references provide all the necessary teachings to motivate one skilled in the art to use LCR sequences in vectors that do not involve integration into the host cell chromosome (thereby eliminating

position effects), and in vectors that are present at greater than one copy per cell. One of skill in the art would immediately recognize that episomal vectors have the requisite properties.

Applicants argue that the Examiner appears to be relying upon the virtues of Applicants' invention to support the obviousness rejection. However, the cited art provides the requisite teachings for putting the genes encoding the proteins essential for replication on a separate piece of DNA from the DNA comprising the expression construct. Svensson et al. (1996) teach that replication-defective viruses, such as replication-defective adenoviruses (RdAd), are useful for gene delivery because they are relatively safe due to their inability to replicate *in vivo*, and can still be generated in very high concentrations by replicating them in cells that express the gene products essential for replication (e.g. the E1 gene products essential for replication of adenoviruses). Following infection, the adenovirus is maintained as a linear episome. Thus the reference teaches the concept of using an episomal vector carrying a transgene while the replication factors are encoded on a separate piece of DNA; in this case, the genomic DNA of the cell. Applicants have not addressed this stated grounds for the rejection (pp. 10-11 of Paper No. 5).

Claim 23 is rejected under 35 U.S.C. 103(a), for reasons of record advanced on pages 11-12 of the previous Office Action (Paper No. 5), as being unpatentable over Yates et al. (1985), Sadelain et al. (1995), Greaves et al. (1989), Grosveld et al. (1987), Ustav et al. (1991), and Svensson et al. (1996) as applied to claims 1-3, 5-14, and 16-21 above, and further in view of Chapman et al. (1991).

Applicants argue that, with regard to the rejection of Claim 23, the deficiencies of the references cited for Claims 1-3, 5-14, and 16-21, are not overcome by the reference of Chapman et al. However, the alleged deficiencies of the references cited for Claims 1-3, 5-14, and 16-21 are discussed above and are applied here as well. Chapman et al. (1991) is only cited for the teaching that it is common practice to transfect cultured

host cells for the *in vitro* expression of a protein of interest. Therefore, it would have been obvious to one of skill in the art at the time of the invention to have made recombinant constructs of the type claimed and to have used them to express a gene of interest in a host cell in culture. Applicants have not addressed the stated motivation to combine the cited references.

Claim 25 is rejected under 35 U.S.C. 103(a), for reasons of record advanced on pages 11-12 of the previous Office Action (Paper No. 5), as being unpatentable over Yates et al. (1985), Sadelain et al. (1995), Greaves et al. (1989), Grosveld et al. (1987), Ustav et al. (1991), and Svensson et al. (1996) as applied to claims 1-3, 5-14, and 16-21 above, and further in view of Chapman et al. (1991).

Applicants argue that, with regard to the rejection of Claim 25, the deficiencies of the references cited for Claims 1-3, 5-14, and 16-21, are not overcome by the reference of Chapman et al. However, the alleged deficiencies of the references cited for Claims 1-3, 5-14, and 16-21 are discussed above and are applied here as well. Applicants argue that Chapman et al. (1991) does not suggest testing candidate regulatory elements, much less LCRs. However, this is precisely what Chapman et al. does in the reference. Chapman et al. test the effect and function of a genetic regulatory element, intron A from human cytomegalovirus immediate early gene, on heterologous expression in mammalian cells. The stated motivation for combining the references is as follows:

> Since it is common practice to assess the function of genetic regulatory elements in transfected cell lines, wherein the regulatory element is operably linked to a marker gene, as disclosed by Chapman et al., one skilled in the art would have been motivated to construct an episomal expression vector of the type claimed using candidate LCR sequences to assess the capability of the genetic element to direct tissue-restricted expression of a linked gene. One would have anticipated a reasonable expectation of success because assessing the function of genetic regulatory elements in cultured cell lines is routine experimentation and only standard molecular biology techniques and standard culture techniques are required to perform the requisite assays. Therefore, it would have been obvious to one of skill in the art

at the time of the invention to have made recombinant constructs of the type claimed using candidate LCR sequences linked to a marker gene to look assess the capacity of the LCR sequence to direct tissue-restricted expression of the marker gene.

One would have been motivated to have combined the teachings of Yates et al., Sadelain et al., Greaves et al., Grosveld et al., Ustav et al., Svensson et al., and Chapman et al. in order to develop test constructs that could be assayed for function in cultured host cells.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention. (Page 13 of Paper No. 5).

Applicants do not address the stated motivation for combining the cited references.

Conclusion

Claims 4 and 15 are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.

Jasemine C. Chambers

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